HIV AND HEPATITIS C: ENTERING A NEW ERA

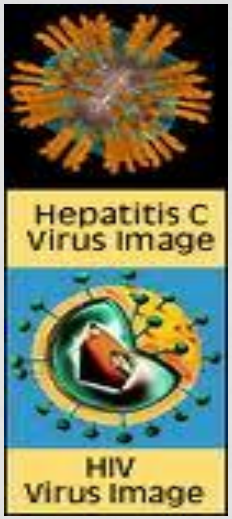
A.CHRISTINE TEAGUE, PHARMD, MPH,AAHIVP
CAMC RYAN WHITE PART C PROGRAM DIRECTOR

HIV CO-MORBIDITIES

- Neuropsychiatric Complications
  - Depression, bipolar disorder, anxiety disorders, cognitive dysfunction
- Metabolic and Renal Complications
  - Lipid changes, insulin resistance, fat redistribution ➞ CAD, DM
  - Kidney dysfunction
  - Osteopenia/porosis/necrosis
- Malignancies
- Chronic Viral Hepatitis Co-Infections
  - Hepatitis B and C

VIRAL HEPATITIS CO-INFECTIONS

- **Hepatitis A**
  - Fecal-oral route
  - Usually self-limited
  - Prevention with vaccine
- **Hepatitis B**
  - Infected blood/body fluids
  - 10% of HIV patients chronically infected
  - Increased risk of liver-related disease and deaths
  - Prevention with vaccine, some ARV agents can be used to treat (3TC, FTC, tenofovir)
- **Hepatitis C**



HIV/HCV PATIENTS HAVE SIGNIFICANT COMORBIDITIES

	HIV	HIV/HCV
Drug disorder	22%	58%
Alcohol disorder	24%	56%
Depression	28%	43%
Bipolar	6%	12%
Anemia	19%	27%
COPD	17%	21%
Hypertension	37%	42%

Goulet JL et al. AIDS 2005;19:S99-105.

WORLDWIDE PREVALENCE OF HCV

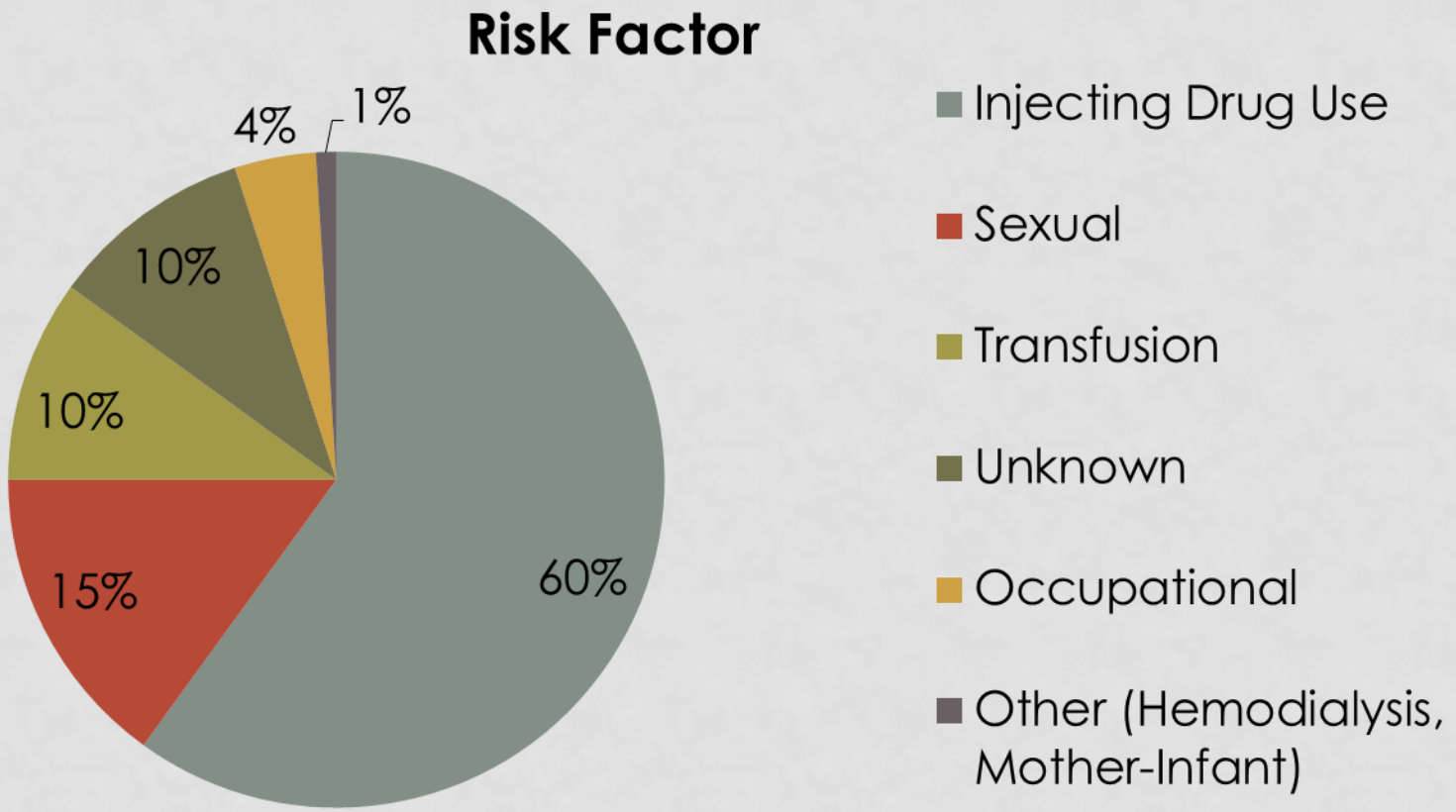
- Estimated 180 million infected worldwide
  - 60 million Russia
  - 32 million Africa
  - 30 million China
  - 20 million Eastern Europe/Middle East

  → **75% of cases**

  - 10 million South America
  - 9 million Western Europe
  - 4-5 million USA ~ 300,000 HIV/HCV co-infected
    - Prevalence about 2% in general population
    - Among those infected 10-30 yrs ago, nearly 75% undiagnosed
    - 15,000 deaths per year
    - Leading cause of deaths from liver disease and liver transplant

Armstrong GL et al. Ann Intern Med 2006;144:705-14.
AASLD Practice Guidelines. Ghany MG et al. Hepatology April 2009.

SOURCES OF NEWLY DIAGNOSED HCV INFECTION



Source: Centers for Disease Control and Prevention

SEXUAL TRANSMISSION OF HCV

- Virus load (HCV RNA) in semen/vaginal secretions
- Risk of HCV transmission by sexual contact
  - Long-term monogamous partnerships: 0.6%/yr
  - Multiple partners/at risk for STDs: 1.8%/yr
- HIV infection increases rate of sexual transmission
- Recent rise in cases of acute HCV cases, especially among MSM

Terrault N. Hepatology 2002;36:S99-105

SEXUAL TRANSMISSION OF HCV

- Recent data presented at CROI 2012
- Swiss HIV Cohort Study, over 6,500 patients
- Twice as many HIV+ gay men infected compared to HIV+ injecting drug users
- 3,333 MSM followed
  - Incidence of new HCV infections in 2011 compared to 1998 increased **18-fold**
- Identified risk factors
  - Unsafe anal sex
  - History of syphilis
  - Chronic HBV infection

19th CROI 2012 Abstract 743

HCV SCREENING RECOMMENDATIONS

- IDU in recent and/or remote past even if only once
- Persons with associated conditions*
- Prior recipients of transfusions or transplants prior to July 1992
- Children born to HCV + mothers
- Health care, emergency medical and public safety workers after an exposure
- Current sexual partners of HCV-infected persons
- Persons born between 1945-1965

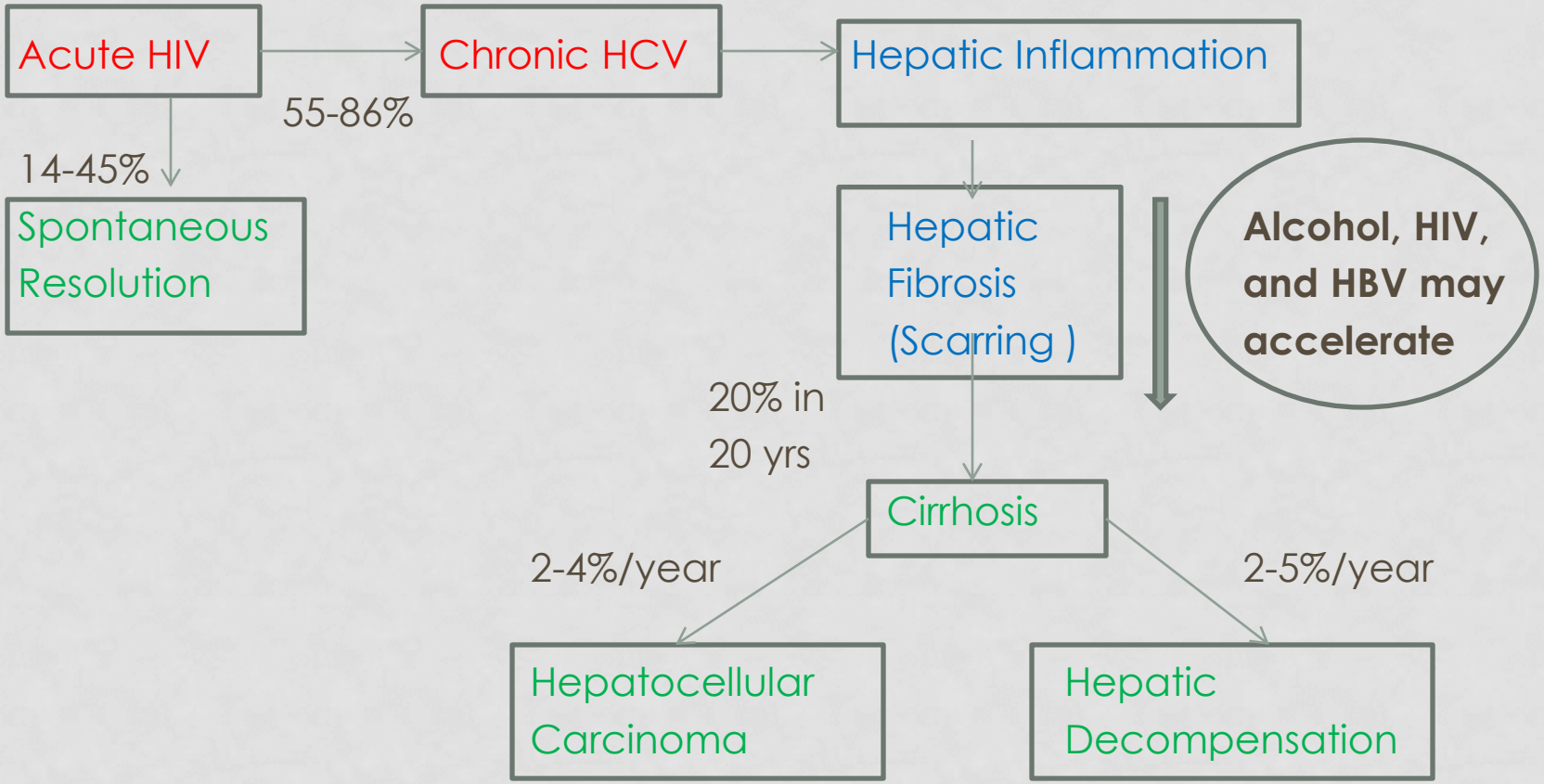
Source: Centers for Disease Control and Prevention

HCV-ASSOCIATED CONDITIONS*

- HIV infection
- Hemophiliacs who received clotting factors prior to 1987
- Persons who have ever received hemodialysis
- Persons who have unexplained abnormal liver enzyme levels

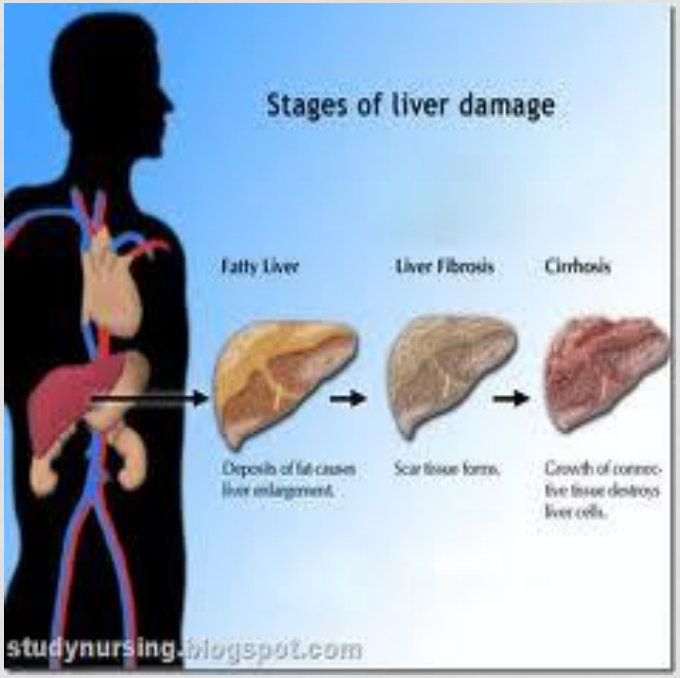
Source: Centers for Disease Control and Prevention

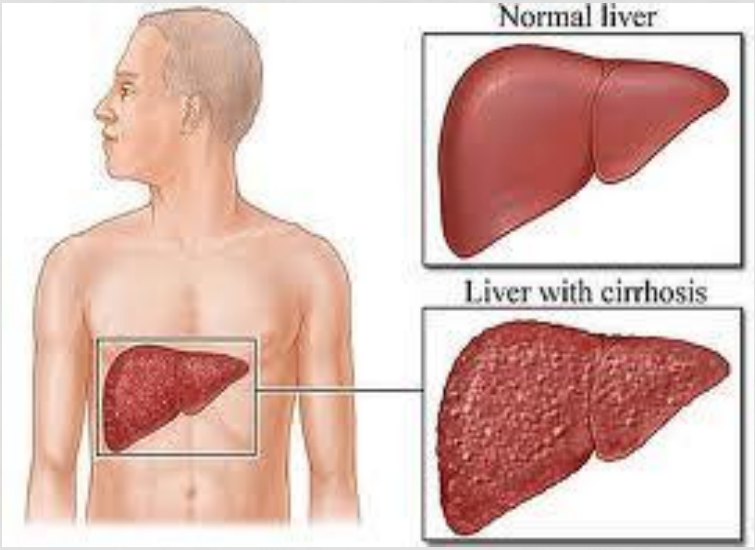
NATURAL HISTORY OF HCV INFECTION



Seef LB. Hepatology 2002;36 (suppl 1):S35-46

STAGES OF LIVER DISEASE





EPIDEMIOLOGY OF HCV IN HIV

- ARV therapy has decreased HIV-related complications
- Prolonged survival of HIV patients
- Chronic HCV is common in HIV patients
  - 25-35% of HIV patients are co-infected
  - In IDU or hemophiliacs, up to 80% co-infected
  - 300,000 patients in the U.S.
- HIV increases mortality in those coinfected with HCV, but not necessarly vice versa

Pol S and Soriano V. Clin Infect Dis 2008;47:94-101.

IMPACT OF HIV ON HCV

- Decreased clearance of HCV
- Increased HCV RNA levels
- Increased risk of cirrhosis
- Increased risk of end-stage liver disease
- Increase risk of liver cancer

- Predictors of severe liver fibrosis
  - Older age (>35 yrs), excessive alcohol consumption (>50g/day), and CD4 <500

Martin-Carbonero L et al. Clin Infect Dis 2004;38:128-33.

HCV COINFECTION AND MORTALITY IN HIV PATIENTS

- Liver disease is the second leading cause of death
- Liver disease is primarily caused by viral hepatitis
- Liver deaths occur at higher CD4 counts and despite ARV therapy

D:A:D Study. Arch Intern Med 2006:166:1632-41.

HCV EVALUATION

- **Patient history**
  - Depression history, screening
  - Control of diabetes mellitus, complications
  - STD screening
  - Heart disease history, stress tests
  - OTC hepatotoxic drugs
  - History of HAV, HBV vaccination
  - Pregnancy testing if applicable

Sherman K. Clin Infect Dis 2012;55:1236-41

HCV LAB EVALUATION

- **HCV RNA level**
  - Predicts treatment response
  - Does NOT correlate with disease progression
- **HCV genotype**
  - Genetic heterogeneity within population
  - 6 distinct genotypes distributed throughout the world
  - Different HCV treatment responses

Sherman K. Clin Infect Dis 2012;55:1236-41

HCV LAB EVALUATION

- **Other tests:**
  - Liver function blood tests (albumin, bilirubin, INR)
  - ALT, AST levels but may not reflect liver damage
  - CBC
  - HAV past exposure (HAV IgG)
  - HBV screening (HBsAg, anti-HBs)
  - Liver cancer screen (abdominal ultrasound)
  - Urine pregnancy test if applicable

Sherman K. Clin Infect Dis 2012;55:1236-41

HCV GENOTYPE DISTRIBUTION IN U.S.

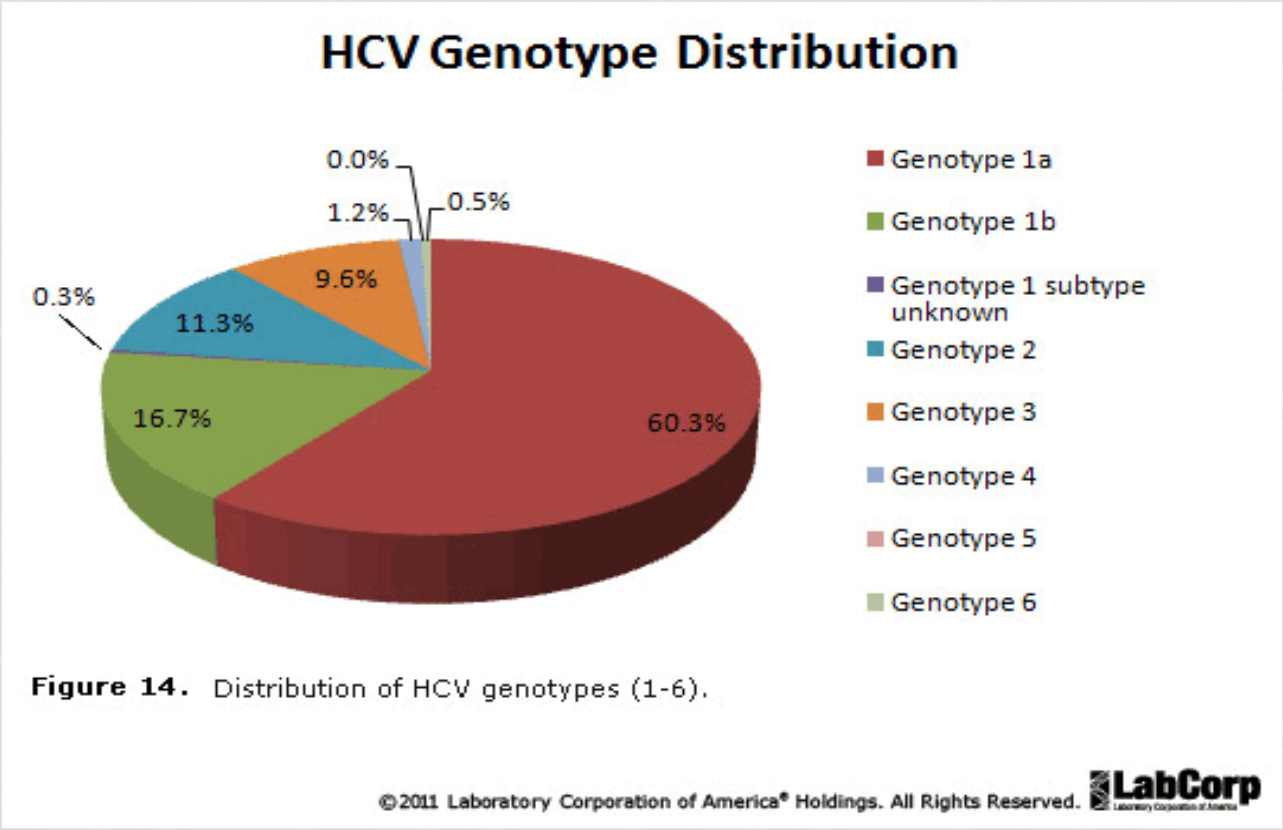


Figure 14. Distribution of HCV genotypes (1-6).

HCV EVALUATION: STAGING LIVER FIBROSIS

- Identify cirrhosis
  - Strongly consider ARV therapy
  - Increased cancer risk
  - Monitor for hepatic decompensation/failure (low albumin and clotting factors, encephalopathy, esophageal varices, portal hypertension)
  - Consider liver transplant evaluation
- Determine cirrhosis by
  - Liver biopsy
  - Non-invasive tests , biomarkers(i.e. FibroSure®)or elasticity echosSherman

K. Clin Infect Dis 2012;55:1236-41

GOALS OF HCV THERAPY

Target Virus → Eradication (Viral Cure) = **SVR** at 6-12 months post tx

Target Disease: Prevent Complications → Delay Cirrhosis

Target Disease: Prevent Complications → Prevent Liver Cancer

Pearlman BL et al. Clin Infect Dis 2011;52:889-900.

FACTORS ASSOCIATED WITH BETTER RESPONSE TO HCV THERAPY

- Genetics: Interleukin-28b gene
- Female sex
- Non-black
- Younger age
- No Obesity
- Absence of HIV co-infection
- Abstaining from alcohol
- Adherence, adherence, adherence

→ **PREDICTS SVR**

TIME POINTS FOR ASSESSMENT OF HCV VIROLOGIC RESPONSE

- **Week 4**: RVR (rapid virologic response) = undetectable HCV RNA
- **Week 12**:
  - Early virologic response (EVR) = 2 log drop in HCV RNA
  - Extended RVR (eRVR) = undetectable HCV RNA
- **Week 24**: undetectable HCV RNA
- **Week 48**: end-of-treatment undetectable HCV RNA
- **Week 72**: SVR (sustained virologic response) = undetectable HCV RNA = cure

Ghany MG et al. AASLD HCV Practice Guideline Update. Hepatology 2011; 54(4): 1433-44

INDICATIONS FOR HCV THERAPY

- HCV RNA +
- Chronic hepatitis with significant fibrosis
- Compensated liver disease (healthy bilirubin, INR, albumin, platelet count, no ascites or encephalopathy)
- Acceptable hematological and biochemical markers (hemoglobin, ANC, creatinine)
- HIV coinfection
  - Increases rate of fibrosis, so consider strongly
- Willingness to be treated and to adhere to treatment requirements

CONTRAINDICATIONS TO HCV THERAPY

- Active depression/psychosis
  - Hospitalization within prior year
  - Suicide attempt within prior year (some use ever)
- Decompensated cirrhosis
- Solid organ transplant (kidney, heart, lung)
- Severe coexisting medical condition (i.e. severe HTN, heart failure, COPD, poorly controlled DM, significant CAD)
- Pregnancy
- Untreated thyroid disease
- Age under 2 years (new PIs not approved for <18)

WHICH PATIENTS SHOULD BE TREATED?

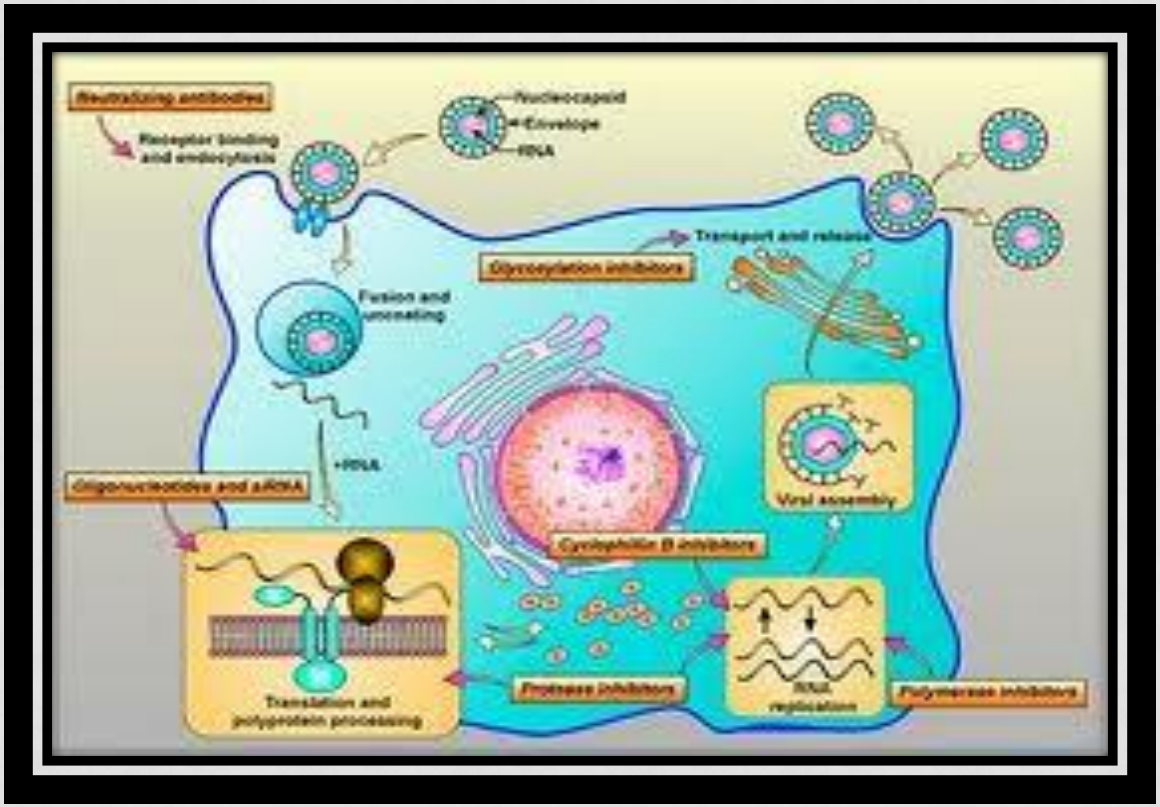
Disease Progression

Treatment Response

Adverse Effects

Competing Comorbities

HCV VIRAL LIFE CYCLE



HCV ANTIVIRAL AGENTS

- **Indirect Acting Agents**
  - Peginterferon (PEG-IFN) alfa
  - Ribavirin
- **Direct Acting Agents** (work directly on viral life cycle)- 27/6 phase III
  - NS3/4 Protease Inhibitors – only active genotype 1
    - Boceprevir, Telaprevir, Simeprevir*,multiple others*
  - NS5A Protein Inhibitors*
    - Daclatasvir
  - NS5B Polymerase Inhibitors*
    - Nucleoside and Non-nucleoside analogues
      - Sofosbuvir, multiple others
  - Cyclophilin Inhibitors*

* Non FDA-approved

HCV TREATMENT WITH HIV CO-INFECTION 2012

Genotype	Therapeutic Option	Duration
1	PEG-IFN-2b + Riba + Boceprevir	48 wks
	PEG-IFN – 2a + Riba + Telapravir	48 wks
2,3	PEG-IFN-2a or 2b + Ribavirin	48 wks
4	PEG-IFN-2a or 2b + Ribavirin	48 wks

Ghany et al. AASLD HCV Practice Guideline Update. Hepatology 2011; 54(4):1433-44.

PEG-INTERFERON + RIBAVIRIN

- **Pegylated IFN- alfa**
  - Suppress viral replication
  - Two formulations: 2a, 2b
    - Alfa -2a: 180 mcg/wk SQ
    - Alfa-2b: 1.5mcg/kg/wk SQ

PEG-IFN-alfa-2a (Pegasys®)

PEG-IFN-alfa-2b (PegIntron®)

- **Ribavirin**
  - Nucleoside analogue
  - Genotype 1,4:
    - ≤ 75 kg: 1,000 mg/d
    - > 75 kg: 1,200mg/d
  - Genotype 2,3: 800 mg/d

Copegus®

Rebetol®

TELAPREVIR : HCV GENOTYPE 1

- NS3/4A protease inhibitor
- Indicated for genotype 1
- Use with PEG-IFN + ribavirin

*If HCV RNA >1,000 IU/ml at week 4 or 12, stop tx

Telaprevir (INCIVEK®)

- Dosage: 750mg every 8 hrs
  - 375mg tablets
- Administer with 20 gm fat meal

INCIVEK® labeling information, Vertex Pharmaceuticals, 2011

TELAPREVIR AND FATTY FOOD

Each telaprevir dose should be taken with food containing **20gms of fat**, such as

- Bagel with cream cheese
- 3 tbsp peanut butter
- 2 oz American or cheddar cheese
- 2 oz potato chips (about 30 chips)
- 1 cup ice cream
- ½ cup trail mix
- ½ cup nuts

Yee HS. Hepatitis C Treatment. The Rx Consultant. 2012; 21(2):1-8

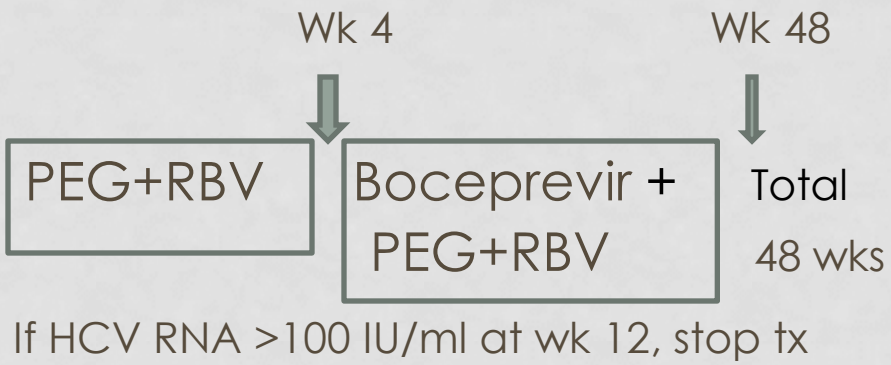
SVR RATES WITH TELAPREVIR FOR HCV GENOTYPE 1

Trial	Arms	SVR
ADVANCE (Naïve)	TVR/PR x 12wks →PR x 12 wks	89%
	TVR/PR x 12wks →PR x 36 wks	75%
	PR x 48wks	44%
PROVE-2 (Prior Rx)	TVR/PR x 12wks→PR x 12wks	51%
	TVR/PR x 24wks →PR x 24wks	53%
	PR x 48 wks	14%

Jacobsen IM et al. N Engl J Med 2011;364:2405-16
Zeuzem S et al. N Engl J Med 2011; 364:2417-28

BOCEPREVIR: HCV GENOTYPE 1

- NS3/4A protease inhibitor
- Indicated for genotype 1
- Use with PEG-IFN + ribavirin



Boceprevir (Victrelis®)

- Dosage: 800mg every 8 hrs
  - 200mg capsules

Victrelis® labeling information, Roche Pharmaeuticals, 2011

SVR RATES WITH BOCEPREVIR FOR GENOTYPE 1

Trial	Arms	SVR
SPRINT-2 (Naïve)	PR x 4wks→BOC/PR x 24wk →PR x 20wk	63%
	PR x 4wks →BOC/PR x 44 wk	66%
	PR x 48wk	38%
RESPOND-2 (Prior Rx)	PR x 4wks→BOC/PR x 32wk → PR x 12wk	59%
	PR x 4 wks →BOC/PR x 44 wk →PR x 44wk	66%
	PR x 48 wks	21%

Poordad F et al. N Engl J Med 2011;364:1195-206
Bacon BR et al. N Engl J Med 2011; 364:1207-17

SVR RATES IN HIV/HCV CO-INFECTION

- PEG-IFN + RBV

	APRICOT[1]	ACTG 5071[2]
Genotype 1	29%	14%
Genotype 2,3	62%	73%

- TVR + PEG-IFN + RBV[3]

	SVR 12 wk data
TVR +PR	74%
PR	45%

- BOC + PEG-IFN +RBV[4]

	SVR 12 wk data
BOC +PR	61%
PR	27%

1. Chung RT et al. N Engl J Med 2004;351:451-9
2. Torriani FJ et al. N Engl J Med 2004:3351:438-50
3. Dietrich D et al. 19th CROI 2012 Abst 46
4. Sulkowski M et al. 19th CROI 2012 Abst 47

ADVERSE EFFECTS OF HCV THERAPY

- Almost all treated will experience something
- Major reason for discontinuing meds (~ 25-30%)
- Interferons
  - Flu-like symptoms (fatigue, headache, fever, rigors)- 50%
  - Loss of appetite and weight loss -40%
  - Mild to moderate hair loss, rashes – 20%
  - Psychiatric (depression, irritability, insomnia, suicidal ideas)-20%
  - Lab abnormalities (drop in cell counts)- 20-25%
  - Thyroid disorders
- Ribavirin
  - Anemia – 20-25%
  - Birth defects

Slim J. Infect Dis Clin N Amer 2012;26:917-29

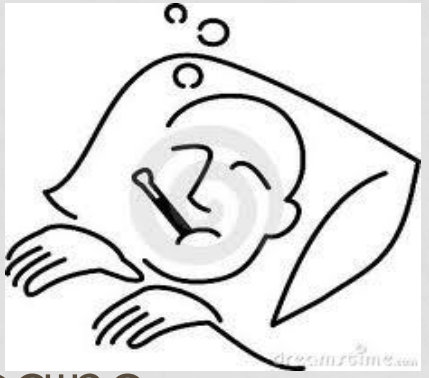
ADVERSE EFFECTS OF HCV PROTEASE INHIBITORS IN HIV/HCV

Telapravir[1]			Boceprevir[2]		
	TVR+PR	PR		BOC+PR	PR
Itching	39%	9%	Anemia	41%	26%
Headache	37%	27%	Fever	36%	21%
Nausea	3%	23%	Fatigue	34%	24%
Rash	34%	23%	Decr appetite	34%	18%
Fever	21%	9%	Diarrhea	28%	18%
Depression	21%	9%	Bad taste	28%	15%
Neutropenia	24%	23%	Vomiting	28%	15%
Anemia	39%	27%	Flu-like	25%	38%
Insomnia	13%	23%	Neutropenia	19%	6%
Decr appetite	11%	18%	Erythropoeitin	38%	21%
Decr weight	13%	23%			

1. Dietrich E et al. CROI 2012 Abstr 46% 2. Sulkowski M et al. 29th CROI 2012 Abst 47

MANAGING TOXICITIES

- **Close follow up**: have patients call with concerning events
- Rash: assessment, antihistamines, topical steroids
- Flu-like symptoms: NSAIDs, hydration
- Depression: B-med referral, antidepressants
- Weight loss: appetite stimulants (Megace®, Marinol®)
- Anal discomfort: topical steroids, lidocaine
- Anemia: decr ribavirin dose, erythropoetin



Slim J. Infect Dis Clin N Amer 2012;26:917-29

SELECTED DRUG INTERACTIONS WITH HCV PROTEASE INHIBITORS

- Anticonvulsants
- Antidepressants
- Benzodiazepines
- Calcium channel blockers
- Colchicine
- Systemic steroids
- Ergot derivatives
- Statins
- Opioids, methadone
- Oral contraceptives
- Erectile dysfunction agents
- St. Johns Wort
- Warfarin
- Zolpidem

INCIVEK® labeling information, Vertex Pharmaceuticals, 2011
Victrelis® labeling information, Roche Pharmaeuticals, 2011

NRTI CHOICE WITH HCV THERAPY

- Avoid zidovudine (AZT) with ribavirin
  - Greater decrease in hemoglobin → higher risk of anemia
- Avoid didanosine (ddI) with ribavirin
  - Risk of mitochrondrial toxicity → lactic acidosis, peripheral neuropathy, pancreatitis
- Questions remain with abacavir
  - May compete intracellularly with ribavirin → decrease ribavirin effectiveness?

Yee HS. Hepatitis C Treatment. The Rx Consultant. 2012; 21(2):1-8

HCV PI AND ARV DRUG INTERACTIONS

- Phase 1 studies in healthy volunteers
- Telaprevir drug levels:
  - Decr 30-50% with lopinavir, darunavir, fosamprenavir
  - Decr with efavirenz (requires incr. dosage)
  - No change with tenofovir, raltegravir
- Boceprevir drug levels:
  - Decr 40% on efavirenz, PIs
  - No change with tenofovir, raltegravir

MEASURES TO AVOID HCV TRANSMISSION

- Avoid sharing toothbrushes, nail clippers and dental or shaving equipment, and be cautioned to cover any bleeding wounds
- Stop using illicit drugs. If continued, avoid reusing or sharing "works", use safe disposal
- Do not donate blood, body organs, tissue or semen
- Practice safe sex by using condoms

Source: Centers for Disease Control and Prevention

SOME OTC AND HERBAL SUPPLEMENTS THAT MAY CAUSE LIVER DAMAGE

- **Acetaminophen**
- Black cohosh
- Chinese herbal medicines
  - Chaso, Onshido, Sho (do)-saiko-to, Jin Bu Huan, Ma Huang (ephedra)
- Kava
- Mistletoe
- Pennyroyral
- Skullcap
- Valerian

Yee HS. Hepatitis C Treatment. The Rx Consultant. 2012; 21(2):1-8

INTEGRATING HEPATITIS C CARE INTO HIV PRACTICE

- Multidisciplinary management team
- Provide support and education
- Treat psychiatric co-morbidities/substance abuse
- Vaccinate against Hepatitis A and B
- Counsel regarding ways to avoid transmission, especially safer sex/condom use and IDU
- Avoid other hepatotoxins, including alcohol, acetaminophen and certain herbal meds
- Provide HCV therapy
- Focus on adherence!!!

CAMC RYAN WHITE HIV PROGRAM

Contact Information: Call toll free 1-877-565-4423
www.camc.org/ryanwhite

HEPATITIS AWARENESS

May 19th is National Hepatitis Testing Day